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PHENOXYTHIOCARBONYLATION AND DEOXYGENATION OF ARYL TRIFLUOROMETHYL CARBINOLS

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Methods for the selective replacement of the OH group by H are very useful in organic transformations and the preparation of biologically active compounds. The most commonly used method for deoxygenation is the catalytic reduction under acidic conditions. However, deoxygenation does not take place when CF_3 is attached at the benzylic carbon. This could be due to the electron-withdrawing property of CF_3, which destabilizes the carbonium ion intermediate. Thus, free radical reactions were selected for reductive cleavage of the C-O Bond. The thiocarbonylation of secondary alcohols and tertiary alcohols carrying an imidazole moiety at the 4-position, followed by the homolytic deoxygenation, yields the deoxygenated products in good yield.

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PREFACE

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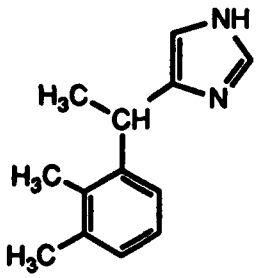
PHENOXYTHIOCARBONYLATION AND DEOXYGENATION OF ARYL TRIFLUOROMETHYL CARBINOLS

1. INTRODUCTION

The benzylic or arylmethyl alcohol moiety is readily accessible *via* the reaction of aryl aldehydes or ketones with carbanion equivalent reagents or by the reaction of arylmetal reagents and carbonyl compounds. The combination of aryl and benzylic hydroxyl functionalities coupled with an amino group has become a major pharmacophore in many medicinal compounds. In addition, benzylic alcohols have been shown to be versatile intermediates for chemical manipulations.

The hydrogenolysis of benzylic alcohols using catalytic hydrogenation provides a mild and effective method to produce the corresponding deoxygenated product.[1,2] This procedure has been commonly used by medicinal chemists for structure-activity relationship (SAR) studies of biologically interesting molecules.

Recently, we prepared the naphthalene analog **2** and found it has α_2-adrenergic agonist activity similar to medetomidine (**1**).[3] Therefore, a series of naphthalene analogs were synthesized for SAR studies. One of the compounds we wanted to prepare was the trifluoromethyl analog **3**. This paper discusses the chemistry of the reductive deoxygenation of aryl trifluoromethyl carbinols and the preparation of **3** from its protected precursor alcohol **5**.[4]



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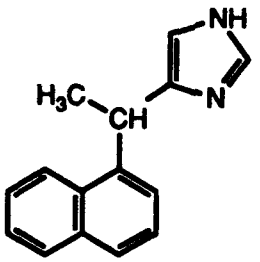

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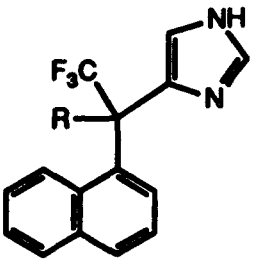


3 R = H

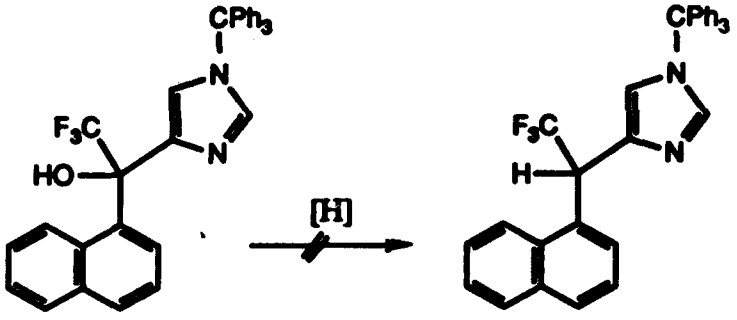
4 R = OH

2. CHEMISTRY

The development of trifluoromethyltrimethylsilane by Olah *et al.*[5] made trifluoromethyl carbinols readily accessible. Although the deoxygenation of benzylic alcohols is well documented[1,2], the deoxygenation of aryl trifluoromethyl carbinols has not been reported. We were interested in this chemical transformation to prepare **3** from the corresponding alcohol **5** for biological evaluation in comparison with the parent

Scheme 1

Attempted Deoxygenation of 5



5 6

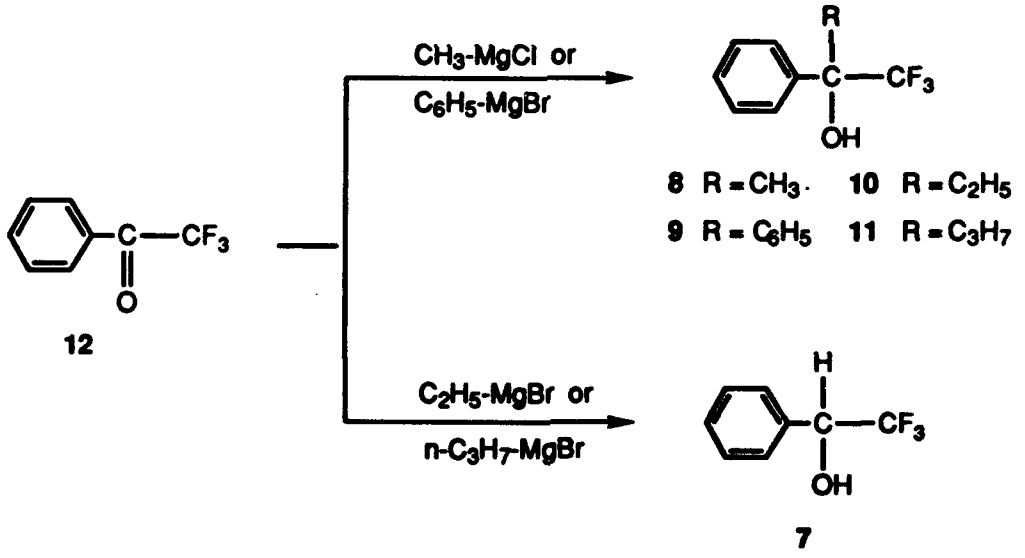
Reaction Conditions	Results
Et_3SiH CF_3COOH	S.M.
H_2, Pd/C CF_3COOH	S.M.
H_2, Pd black CF_3COOH	S.M.
H_2/PtO_2 CF_3COOH	mixture
Li/NH_3	mixture

compound 2. Several attempts to prepare 3 from 5 under a variety of catalytic hydrogenation conditions failed to produce the desired deoxygenation product as shown in Scheme 1. The hydrogenation of 5 in ethanol using a variety of catalysts gave only starting material, even when a small amount of hydrochloric acid was added. When trifluoroacetic acid or acetic acid were used as a solvent, partial ring reductions were observed. The difficulty encountered in effecting the 5 to 6 transformation was attributed to the presence of the trifluoromethyl group. It is known that the rate of hydrogenolysis of benzyl-oxygen compounds increases in the order OH < O-alkyl << O-aryl < OH^+-alkyl < OH_2^+ < OAc < $OCOCF_3$.[1] The ease of displacement parallels the leaving group ability of the substituents (the ability to bear a negative charge). Due to the inductive effect of the trifluoromethyl group, the protonation of the benzyl alcohol functionality

would be impeded and formation of a carbocation or carbocation-like intermediate would be unfavorable. Thus, catalytic reduction procedures fail to yield deoxygenated products. Therefore, a reductive deoxygenation procedure that proceeds through a free-radical mechanism was attempted.

Many reagents have been developed for such a homolytic cleavage of C-O bonds.[6] We chose the Robins procedure[7] for this study because of its mild conditions and effective conversion to the deoxygenated products. To study the homolytic cleavage of the C-O bond of **5**, model compounds **7** (a secondary alcohol), **8** and **9** (tertiary alcohols) were used (Scheme 2). Compound **7** is the simplest benzyl alcohol and is commercially available. Compounds **8** and **9** were prepared from 2,2,2-trifluoroacetophenone (**12**) and the corresponding methyl- or phenylmagnesium bromide. Compound **10** and **11** were to be included in the study and an attempt was made to synthesize them through the reaction of **12** with ethyl- or n-propylmagnesium bromide. However, when **12** was treated with ethyl- or n-propylmagnesium bromide in refluxing tetrahydrofuran, only the reduced alcohol **7** was isolated. It is known that reduction of the ketone is a side reaction of the Grignard reaction, especially when a β-hydrogen is present in the Grignard reagent. To our surprise, only reduction, and no nucleophilic addition, was detected.

Scheme 2



8 R = CH_3 **10** R = C_2H_5

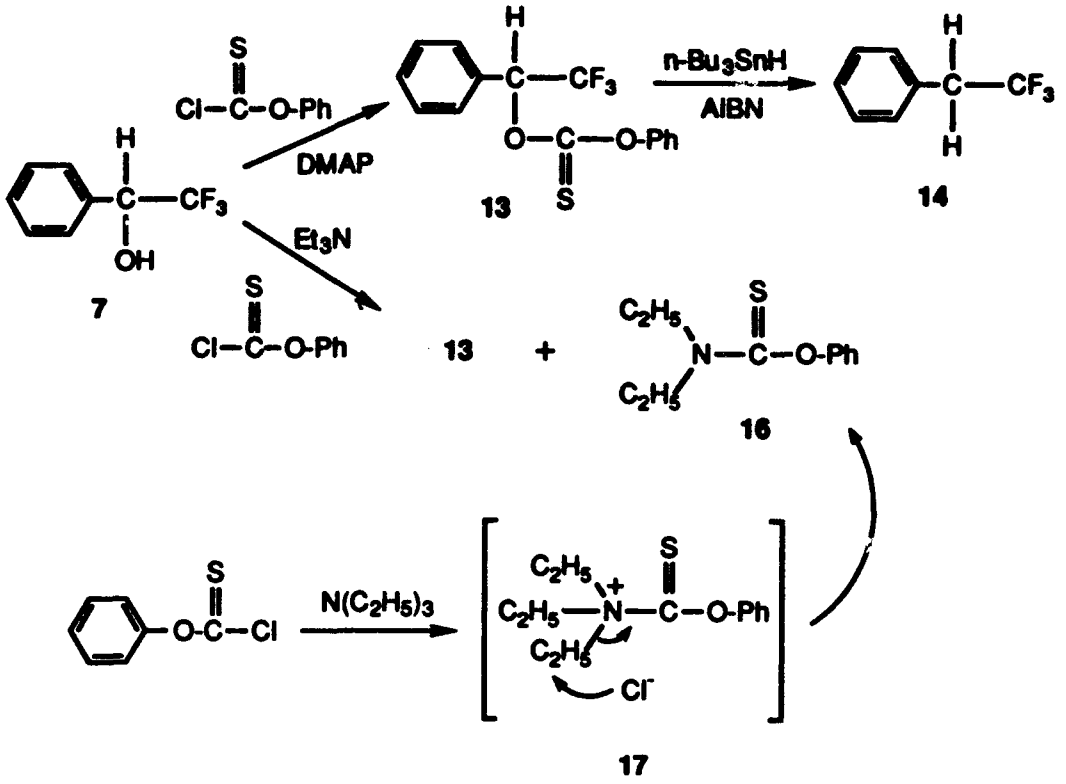
9 R = C_6H_5 **11** R = C_3H_7

12

7

Compound **7** reacted with phenyl chlorothionoformate (PTC-Cl) and 4-dimethylaminopyridine (DMAP) in acetonitrile (CH_3CN) very smoothly to give **13** along with a small amount of the symmetrical diphenylthiocarbonate **15** as a by-product (Scheme 3). Interestingly, when triethylamine was used as the acid scavenger, in addition to the desired product **13**, a major side product **16** was isolated in 53% yield. The mechanism of formation of **16** is proposed in Scheme 3. The formation of **16** must be derived from

Scheme 3



attack of the chloride ion at one of the ethyl groups of the charged intermediate **17**. Consequently, it is recommended that a pyridine-type amine shall be used as the base in this reaction. Compound **13** was then smoothly transformed to **14** using tributyltin hydride (n-Bu_3SnH) and 2,2'-azobisisobutyronitrile (AIBN) in toluene. We found ^{19}F NMR spectroscopy was very useful for monitoring these reactions since the fluorine atom is present in the starting material and the product. Thus, the chemical shifts of the fluorine atom and the characteristic of H-F coupling become a very useful

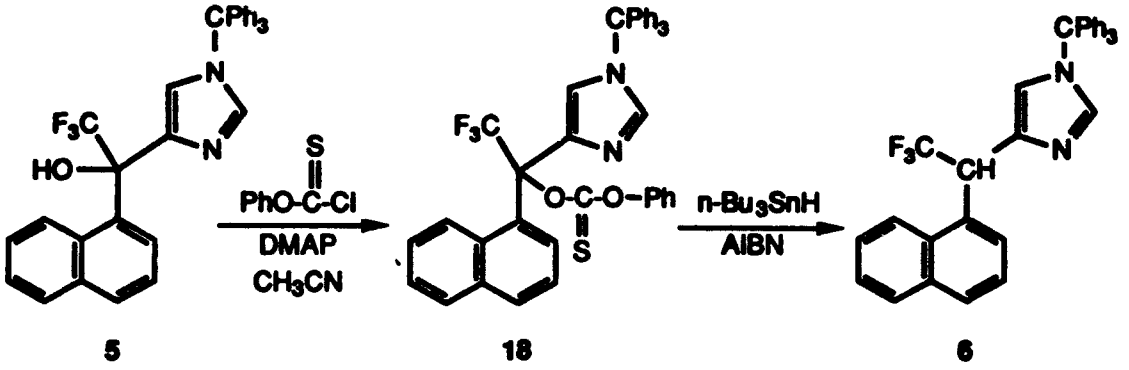
Table 1. Chemical shifts of proton and fluorine NMR

δ (ppm)	7	13	14	3	5
^1H NMR (benzylic-H)	4.98 (q)[a]	6.62 (q)[a]	-	5.80 (q)[a]	-
^{19}F NMR	-78.55 (d)[a]	-75.58 (d)[a]	-66.1 (t)[b]	-66.35 (d)[c]	-74.17 (s)[a]

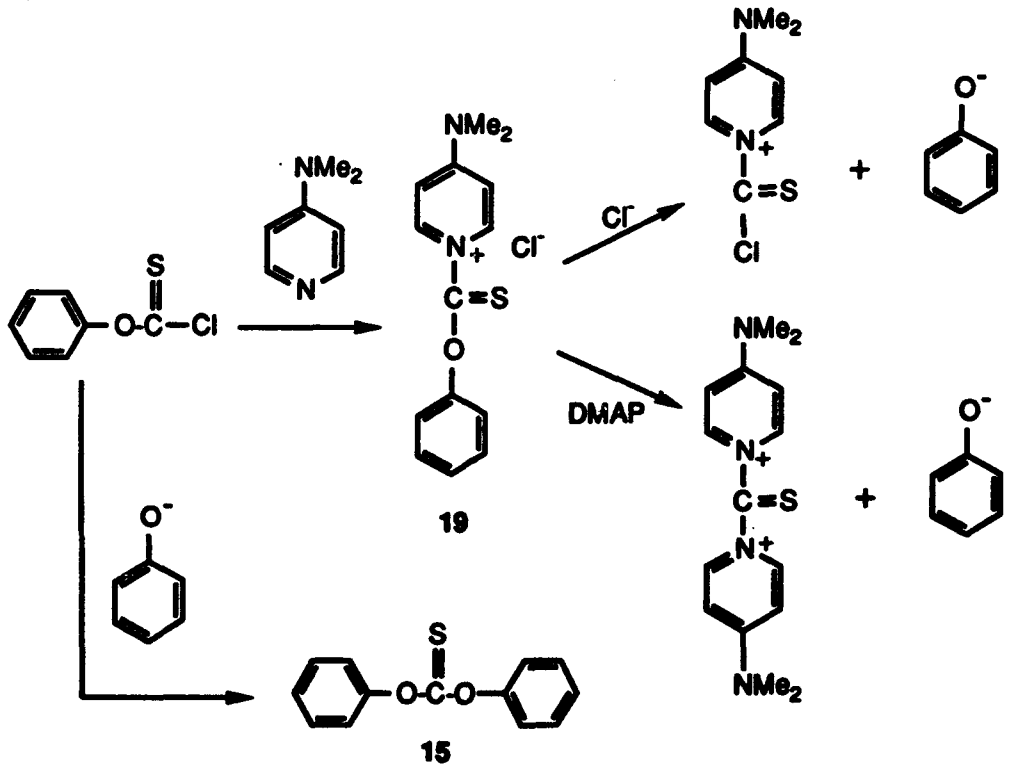
[a]Solvent: $CDCl_3$
[b]Solvent: Toluene
[c]Solvent: CD_3OD

Scheme 4

Free Radical Deoxygenation of 5



Scheme 5



diagnostic tool for these chemical transformations. For instance, the fluorine signal of **7** is a doublet centered at -78.55 ppm due to coupling with the benzylic proton. After deoxygenation the fluorine signal becomes triplet due to coupling with the two benzylic protons as observed in compound **14** (see Table 1).

The reaction of **5** with PTC-Cl and pyridine in methylene chloride (CH_2Cl_2) followed by reductive deoxygenation gave **6** in 66% yield (Scheme 4). To our surprise, the reaction of **8** or **9** with PTC-Cl and DMAP or pyridine in CH_3CN or CH_2Cl_2 gave only starting material and **15**. Compound **15** was also formed without the presence of **8** or **9** under these conditions. It appears that the hindered alcohols **8** and **9** react either very slowly or do not react with the adduct of DMAP-(PTC-Cl) (**19**). Thus, intermediate **19** reacts with DMAP, or chloride ion, resulting in the release of phenolate ion which further reacts with PTC-Cl to produce **15** as shown in Scheme 5. To examine the possibility of any electronic factor involved in this reaction, we substituted **7** with 2-phenyl-2-propanol for phenoxythiocarbonylation. Under the identical conditions, the destrifluoro tertiary alcohol did not react to produce any thionocarbonate ester. Thus, the difficulty of conversion of tertiary alcohols **8** and **9** to their phenyl thionocarbonate esters must be attributed to steric hindrance at the hydroxyl group. Interestingly, this steric factor was not observed in the reaction of **5** with PTC-Cl.

3. EXPERIMENTAL METHODS

Melting points were determined using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1420 spectrometer. ^1H NMR spectra were recorded with a Bruker 250 spectrometer using TMS as the internal standard and ^{19}F NMR were referenced to $CFCl_3$. Chemical ionization (CI) mass spectra were obtained on a Finnigan 1015D spectrometer with a Model 6000 data collection system. The composition of the reaction mixtures from various runs was monitored by thin layer chromatography (TLC) on silica gel GF plates (Analtech, Inc., Newark, DE). Flash column chromatography was performed on Merck silica gel 60, 230-400 mesh ASTM. The solvent extracts during work-up were dried over anhydrous sodium sulfate or magnesium sulfate.

3.1 General Procedure for Phenyl Thionocarbonate Esters Synthesis

To a solution of the alcohol (1 mmol) and PTC-Cl (1.1 mmol) in dry CH_3CN or CH_2Cl_2 (2.5 mL) was added DMAP or pyridine (2.2 mmol) at ice-bath temperature under nitrogen. The mixture was stirred at room temperature for 16 hr and TLC was used to monitor the reaction: silica gel, hexane/benzene = 8/3. After the reaction was complete, the precipitate was filtered and washed with the solvent. The filtrate was evaporated and the residue was then dissolved in $CHCl_3$, washed with 1N HCl, saturated $NaHCO_3$,

water, and dried. Evaporation of solvent gave the crude product which was purified by flash column chromatography (silica gel, eluted with hexane followed by benzene).

3.2 1-(Phenyl)-2,2,2-trifluoroethyl Phenyl Thionocarbonate (13) and Phenyl N,N-Diethylthionocarbamate (16)

Method 1. Compound **13** was prepared from **7** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.65 (q, 1H, benzylic-H, J = 6.5 Hz), 7.05-7.52 (m, 10H, ArH); ^{19}F NMR ($CDCl_3$) -75.58 ppm (d, J = 5.0 Hz); MS (CI/NH_3) m/e 313 (MH^+, 50%), 159 (C_6H_5-CH-CF_3^+, 100%).

Method 2. Et_3N was used as the base instead of DMAP in Method 1. Compound **13** was isolated in 29% and the byproduct **16** was obtained in 53% as a brown oil: ^{1}H NMR ($CDCl_3$) δ1.31 (t, 6H, $2CH_3$, , J = 7.0 Hz), 3.67 (q, 2H, CH_2, J = 7.0 Hz), 3.89 (q, 2H, CH_2, J = 7.0 Hz), 7.06 (d, 2H, ArH, J = 8.0 Hz), 7.25 (dd, 1H, ArH, J = 7.5 , 7.5 Hz), 7.39 (d, 2H, ArH, J = 8.0 Hz).

3.3 (2,2,2-Trifluoroethyl)benzene (14)

To a solution of **13** (312 mg, 1 mmol) in toluene (15 mL) was added n-Bu_3SnH (0.4 mL, 437 mg, 1.5 mmol) and AIBN (32 mg, 0.2 mmol) at room temperature. The mixture was degassed with N_2 for 3 min, then heated in an oil-bath at 75-80 °C for 3 hr. The boiling point of **14** was estimated to be close to the solvent, toluene, therefore, the isolation of **14** was not attempted. ^{19}F NMR spectrum was used to determine the extent of the reaction. ^{19}F NMR (toluene, reaction mixture) showed the chemical shift at -75.58 ppm (starting material) disappeared and a new signal at -66.1 ppm (t, J = 11.0 Hz) had appeared, consistent with the formation of **14**.

3.4 (1-Naphthalene)-(2,2,2-trifluoro)-1-[4-(1-triphenylmethyl)imidazole]ethyl Phenyl Thionocarbonate (18)

Compound **18** was obtained as the crude product (1.1 g, 85%) from **5** (1.07 g, 2.0 mmol) in CH_2Cl_2 using pyridine as the base (see Experimental **3.1**): IR (KBr) 1751 cm^{-1} (thionocarbonate); ^{1}H NMR($CDCl_3$) δ 6.78-6.65 (m, 29H, ArH and Im-H); ^{19}F NMR ($CDCl_3$) -67.58 ppm; MS (CI/NH_3) m/e 671 (MH^+, 100%), 243 (Ph_3C^+, 100%).

3.5 4-[1-(1-Naphthalenyl)-2,2,2-trifluoroethyl]-[1-(triphenylmethyl)]imidazole (6)

The crude phenyl thionocarbonate ester **18** (1.06 g, 1.5 mmol) was dissolved in benzene (15 mL) and treated with n-Bu_3SnH (0.6 mL, 2.3 mmol) and AIBN (48 mg, 0.3 mmol) at room temperature. The mixture was then degassed with N_2 for 3 min, then heated in an oil-bath at 75-80 °C for 3 hr. The solvent was evaporated and the residue was chromatographed on silica gel (hexane/EtOAc = 4/1). The product was collected and

recrystallized from ether to afford **6**: (680.8 mg, 66% from **5**): mp 173-174 °C; IR (KBr) 3062, 1492, 1147 1103 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.62 (q, 1H, benzylic-H, J = 9.3 Hz), 6.81 (s, 1H, Im-H), 7.07-7.11 (m, 6H, ArH), 7.27-7.36 (m, 9H, ArH), 7.40 (d, 1H, J = 1.3 Hz), 7.45 (d, 1H, ArH, J = 7.64 Hz), 7.48-7.57 (m, 2H, ArH), 7.68 (d, 1H, J = 7.3 Hz), 7.79-7.88 (m, 2H, ArH), 8.10 (d, 1H, ArH, J = 8.1 Hz); MS m/e calc'd for $C_{34}H_{25}F_3N_2$: 518.1970; Found: 518.1954.

3.6 4-[1-(1-Naphthalenyl)-2,2,2-trifluoroethyl]-1H-Imidazole (3)

To a suspension of **6** (700 mg, 1.35 mmol) was added 60% aqueous CF_3COOH (15 mL). The mixture was stirred for 16 hr and the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 (15 mL) and 10% aqueous HCl (15 mL). The organic layer was then washed with 3x15 mL of 10% aqueous HCl. The combined acidic solution was neutralized to pH 10 and extracted with 4x75 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried and concentrated to yield **3** (250 mg, 67%): mp 186-187 °C; IR (KBr) 3417, 1463, 1251, 1153, 1097 cm^{-1}; ^1H NMR (CD_3OD) δ 5.80 (q, 1H, benzylic-H, J = 9.5 Hz), 7.14 (s, 1H, Im-H), 7.43-7.68 (m, 5H, ArH), 7.87 (t, 2H, ArH, J = 8.84 Hz), 8.20 (d, 1H, ArH, J = 8.41 Hz), ^{13}C NMR (CD_3OD) δ 45.35 (q, 29.14); ^{19}F NMR (CD_3OD) -66.35 ppm (d, J = 8.0 Hz); MS (CI/NH$_3$) m/e 277 (MH+); MS m/e calc'd for $C_{15}H_{11}F_3N_2$: 276.0874; Ffound: 276.0873.

4. CONCLUSION

The thiocarbonylation of a secondary (α-trifluoromethyl)benzyl alcohol **7** proceeds smoothly with phenyl chlorothionoformate to form the phenyl thionocarbonate **13**. The homolytic deoxygenation of **13** occurred cleanly under mild conditions with n-Bu_3SnH and AIBN. Due to the steric hindrance, the tertiary alcohols **8** and **9** did not react with PTC-Cl, even in the presence of DMAP. However, in contrast to the model study, compound **5**, a tertiary alcohol, is converted to the thionocarbonate derivative and then smoothly transformed to **6** by homolytic deoxygenation.

LITERATURE CITED

1. Rylander , P. in "Catalytic Hydrogenation in Organic Syntheses", Academic Press, New York, 1979, pp 271-312.

2. Freifelder, M. in "Catalytic Hydrogenation in Organic Synthesis, Procedures and Commentary", John Wiley & Sons, New York, 1978, pp 107-151.

3. Amemiya, Y.; Hong. S. S.; Venkataraman, B. V.; Patil, P. N.; Shams, G.; Romstedt, K.; Feller, D. R.; Hsu, F.-L.; Miller, D. D. *J. Med. Chem.* **1992**, *35*, 750-7[illegible]

4. The preparation of 4 was described in detail in the manuscript which has been submitted to J. Med. Chem. for review.

5. Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393-395..

6. Hartwig, W. *Tetrahedron* **1983**, *39*, 2609-2645.

7. Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059-4065.